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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,420	MINENO ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,13 and 15-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,13 and 15-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on February 14, 2006.

Preliminary Remark

Claims 1-6, 8-12, 14, 22, and 23 are canceled.

Claims 7, 13, and 15-21 are pending and are under prosecution therefore.

Claim Rejections - 35 USC § 112

The rejection of claims 7-9, 12-21, and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on November 14, 2005 is withdrawn in view of the Amendment received on February 14, 2006.

The scope of enablement rejection of claims 7, 13, and 15-21, under 35 U.S.C. 112, first paragraph, for enabling a method involving a hydrodynamic point-sink shearing fragmentation method, while not enabling a method involving a variety of fragmentation methods, made in the Office Action mailed on November 14, 2005 is withdrawn in view of the Amendment received on February 14, 2006, amending the claims to the enabled scope.

The scope of enablement rejection of claims 8, 9, 12, and 23 under 35 U.S.C. 112, first paragraph, made in the Office Action mailed on November 14, 2005 is withdrawn in view of their cancellation in the Amendment received on February 14, 2006.

Claim Rejections - 35 USC § 103

The rejection of claims 8, 9, and 14 under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Research, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et

al. (PNAS, 1998, vol. 95, pages 4487-4492), made in the Office Action mailed on November 14, 2005 is withdrawn in view of the Amendment received on February 14, 2006, canceling the claims.

The rejection of claims 23 under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Reearch, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et al. (PNAS, 1998, vol. 95, pages 4487-4492) as applied to claims 7-16 above, and further in view of Sorge et al. (U.S. Patent No. 5,556,772, issued September 17, 1996), made in the Office Action mailed on November 14, 2005 is withdrawn in view of the Amendment received on February 14, 2006, canceling the claim.

Rejection, Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 7, 13, 15, and 16 under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Research, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et al. (PNAS, 1998, vol. 95, pages 4487-4492), made in the Office Action mailed on November 14, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on February 14, 2006 have been fully considered but they are not found persuasive.

Applicants' arguments are addressed the same order they were presented in the "Response to Arguments" section.

The Rejection:

Oefener et al. disclose a method of producing a plurality of random DNA fragments via point-sink fragmentation method, which is hydrodynamic (or physical means) in mechanism (page 3880, 1st column, 2nd paragraph).

Oefener et al. disclose that the major advantage of their method produces greater randomness of fragmentation sites and >90% yield fragments over 2-fold size range (page 3876, 2nd column, 2nd paragraph).

While Oefener et al. do not explicitly disclose that the DNA fragments produced by their method has the distribution ratio of 1 to 5 and a size convergence rate of 80% or more, the instant specification explicitly evidences that such method would necessarily produce the DNA fragments of the above-recited characteristics:

> "More concretely, the physical method includes the hydrodynamic point-sink shearing method [Peter J. Oefner et al., *Nucleic Acids Res.*, 24, 3879-3886 (1996);...More concretely, the physical method includes the hydrodynamic point-sink shearing method...In the method for producing a genomic DNA library of the present invention, the ***hydrodynamic point-sink shearing method is preferred from the viewpoint of efficiently obtaining a fragmented DNA which meets the requirements for the distribution ratio, the size convergence rate, and the average size***" (page 16, lines 5-12).

The fragmentation method is disclosed as being "point-sink" (page 3881, 2nd column, bottom paragraph).

The fragmentation (or shearing) method employed by Oefener et al. is disclosed as producing fragments ranging from 298 bps to 12 kbps (see Figure 2).

Oefener et al. do not employ ligation of adapters to their fragmented DNAs followed by an amplification of said adapter ligated DNA fragments via use of primers.

Oefener et al. do not employ PCR method for amplification of the adapter ligated DNA fragments.

Oefener et al. do not employ primers that comprises a sequence complementary to the adapters of the adapter ligated DNA fragments.

Lucito et al. disclose a method of generating a genomic DNA library involving the steps of fragmenting a genomic DNA; ligation of adapters thereto, producing adapter-ligated DNA fragments; followed by the PCR amplification said adapter-ligated DNA fragments (page 4487, 2nd column, 2nd paragraph). The amplification is achieved via use of AmpliTaq, in a thermocylcing reaction, said reaction involving temperatures of 77 and 95°C (page 4487, 2nd column 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Oefener et al. with the teachings of Lucito et al. for the following reasons.

Oefener et al. clearly and explicitly discuss that their method involving random fragmetion of genomic DNA molecules via point-sink flow system is for generating DNA library (page 3876, 1st column, *Introduction*) and subcloning prior to DNA sequence analysis.

While Oefener et al. employ shotgun cloning method in amplifying their fragmented DNA molecules, one of ordinary skill in the art would have been easily motivated to modify the teachings of Oefener et al. with the well-known amplification techniques such as adapter-mediated amplification of Lucito et al., because by doing so, one ordinary skill in the art would have been able amplify DNA fragments for DNA sequence analysis, such as nucleic acid sequencing, AFLP, etc.

One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success at combining the teachings as Oefener et al. already employ the adapter ligation to the DNA fragments. While the artisans employ the adapters for introducing the

adapter-ligated DNA fragments into the vector, one of ordinary skill in the art would have had a reasonable expectation of success at employing primers which were complementary to these adapters for the amplification of the fragments as evidenced Lucito et al.

With regard to the limitation of DNA library maintaining 85% or more copy numbers of a set of genes or sequences on a genomic DNA, since Oefener et al. employ an identical method of fragmenting DNA molecules and as Lucito et al. employ an identical method of adapter-assisted amplification, barring evidence to the contrary, the combination of the method would necessarily produce a DNA library maintaining 85% or more copy numbers of a set of genes.

According to *In re Best* 195 USPQ 430, 1997, the court stated that, "Patent Office can require applicant to prove that prior art products do not necessarily or inherently posses characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant" (pp. 430).

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Initially, on page 8, bottom paragraph of Applicants' response, Applicants state that "[a]ll previous submitted arguments are herein incorporated by reference."

As the previously submitted arguments have been fully rebutted in the previous Office Action (mailed on November 14, 2005), the present Office Action will address the arguments presented in the instant Amendment of record.

Applicants contend that there is "insufficient motivation combine the references of Oefner and Lucito" as suggested by the Office action (page 8, bottom paragraph, Response).

Applicants continue that, "Oefner fails to suggest or disclose the specification [*sic*] amplification primers required by independent claims 7 and 13 of the present invention." (page 8, bottom paragraph to page 9, top paragraph).

The above phrase includes an obvious typographical error, as there is no such "specification amplification primers." It is assumed that Applicants intend to mean, "specific amplification primers."

Applicants arguments are not found persuasive for the following reasons.

Initially, if Applicants are contending that Oefner must explicitly state that specific primers be employed for amplification of the sheared fragments, then Oefner reference would have been cited as being anticipatory reference under 35 U.S.C. 102 (at least for claim 7). However, the claims were rejected under 35 U.S.C. 103(a) obviousness. Whether one of ordinary skill in the art at the time the invention was made would have been motivated to combine the references to arrive at the claimed invention, is the standard of obviousness. Of course, in forming the obviousness, it is not required that reference A, for example, explicitly refer to reference B.

In re Oetiker, 977, F.2d 1443, 1448 (Fed. Cir. 1992) clearly evidences this understanding.

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness **is clearly wrong**.... While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, **it is not necessary that the cited references or prior art specifically suggest making the combination....** In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

The issue, therefore, is whether one of ordinary skill in the art at the time the invention was made would have recognized (thus motivate), "some teaching, reason, suggestion... to combine existing elements to produce," the claimed subject mater.

There exists many different well-known and established means for generating DNA libraries, such as, "passage through the small orifice of a hypodermic needle...a high pressure spray atomizer...nebulization...sonic treatment...stirring in a blender...partial digestion by restriction endonucleases...treatment with DNAse I in the presence of manganese ions." (page 3879, 1st column, 2nd paragraph, Oefner et al.) Oefner et al. explicitly recite that the above-discussed techniques are employed for the purpose of generating random DNA fragments, "for further manipulation and analysis." (page 3879, 1st column, 2nd paragraph).

In addition, the desire to produce DNA libraries is well known and accepted in the art of biotechnology, such as their usefulness in, "shot gun sequencing." (page 3879, 2nd column, 2nd paragraph, Oefner et al.)

Thus, it would go unquestioned that one of ordinary skill in the art at the time the invention was made would have clearly recognized the benefit of producing DNA libraries of random DNA fragments.

Oefner et al. improves the above-discussed methods of generating random DNA fragments by employing point-sink fragmentation method (as discussed above).

The artisans explicitly state that their method produces, "greater randomness of fragmentation sites and a >90% yield of fragments over a 2-fold size range that can be easily pre-selected by varying flow-rate." (page 3879, 2nd column, 2nd paragraph). The artisans of course, demonstrates this fact by controlling the flow rate and producing fragments varying sizes, such as

those which average, "1000 bp in length," (page 3881, 1st column, 2nd paragraph), approximately 300 bp to 48 kbps (see Figure 2). The artisans also clearly demonstrate the versatility of the method:

"At the maximum flow-rate of 8.6 ml/min, fragments ranged in size from ~300 to 600 bp."

"Shearing times >6 min increased the percentage of fragments within a range of 750-1500 bp..." (page 3882, 1st column, 1st and 2nd paragraphs)

While Oefner et al. do not explicitly employ an amplification of the fragments via amplification primers (as recited in claim 7, step (2)) or via ligation of the adaptors and employing primers which hybridize to the adaptors (as recited in claim 13, steps (a)-(c)), such method was well known in the art as well as the desire to do so – Lucito et al. disclose that their method would be useful for "immortalizing and archiving DNA for later analysis from nonrenewable sources." (page 4487, 1st column, 2nd paragraph).

Particularly, the motivation for using an adaptor-assisted amplification technique, as disclosed by Lucito et al., is plainly evident as discussed below.

It is clear from the disclosure of Oefner et al. that the DNA fragments produced by point-shearing method produces random fragments. And because the sequences are random, one of ordinary skill would not have been able to derive a primer which is complementary to these fragments for amplification. Thus, motivation to use an amplification method, which allows amplification of random nucleic acid fragments, would have naturally led one of ordinary skill in the art to consider the well known adaptor-assisted primer amplification, as evidenced by Lucito et al.

In short, adaptor-assisted primer amplification does not require *a priori* knowledge of the nucleic acids, which are to be amplified. The technique employs a ligation of adaptors of known sequences to the DNA fragments, wherein the amplification is achieved by employing primers that

are directed to the adaptors. Since the sequence of the adaptors are known, one can amplify any DNA fragments which had adaptors ligated thereto.

Lucito et al. generates a plurality of nucleic acid fragments which are "representative of genomes," wherein the starting genomic DNA are fragmented with restriction enzymes. The enzymes are chosen so that the cutting of the enzyme produces nucleic acid fragments comprising known ends (page 4487, 2nd column, 2nd paragraph), wherein the ligation of the adaptors allows amplification of the DNA fragments.

Hence, given the teachings of Oefner et al. and Lucito et al., one of ordinary skill in the art at the time the invention was made would have been clearly motivated to employ the technique Oefner et al. for generating DNA libraries with greater randomness, wherein the generated random fragments would have been amplified by adaptor-assisted primer amplification, as disclosed by Lucito et al.

In addition, one of ordinary skill in the art would have had a clear expectation of success at amplifying the random fragments of Oefner et al. with the technique of Lucito et al., given that adaptor-assisted amplification has been commonly employed for amplifying nucleic acid fragments.

Thus, Applicants' argument that there exists no motivation to combine the references is not found persuasive.

Next, Applicants point out that the claims require that, "the mixture of fragment and DNA" is a mixture of DNAs having an average size of from 0.5 kb to 2.5 kb (page 9, 2nd paragraph, Response) and that Oefner et al. fail to suggest or disclose which lengths of fragments would be suitable to maintain copy numbers of a set of genes or sequences on a genomic DNA in case that nucleic acid fragments are amplified by nucleic acid amplification using amplification primers.

This argument is not found persuasive for the following reasons.

Lucito et al., explicitly discusses a problem encountered when amplifying nucleic acid sequences:

> "PCR does not amplify all fragments equally well, and high molecular weight fragments in particular [long fragments] are very poorly amplified." (page 4488, 2nd column, 3rd paragraph).

As evidenced by Lucito et al., the fact that PCR amplification is biased toward shorter fragments as well as the difficulties associated with amplifying long pieces of nucleic acid is known in the art.

Hence, Lucito et al., employ a combination of enzymes so as to generate sufficiently short nucleic acid fragments:

> "Thus...enzymes that cleave frequently were used to prepare HCRs." (page 4488, 2nd column, 3rd paragraph)

Lucito et al. evidences that these shorter fragments, when amplified via adaptors, represented approximately 75% of the genome (or copy number; see page 4489, 1st column, 1st paragraph). Lucito et al. also evidences that their method reproducibly represented approximately 70% of the human genome. (page 4489, 1st column, 2nd paragraph)

While the fragments amplified by Lucito et al. were disclosed as being in the range of 1000 bp (see Figure 1, Lucito et al.), Oefner et al. disclose a method which generated nucleic acid fragments as low as ~300 bps with capability of producing fragments which have 600 bps, which is clearly within the claimed fragment size. Hence, given the fact that PCR is biased toward shorter nucleic acid fragments, one of ordinary skill in the art would been motivated to combine the teachings of Oefner et al. and Lucito et al., so as to generate a DNA library as claimed.

Given that Luicto et al. were able to generate library representing approximately 75% of the genome (or copy number) employing nucleic acid fragments which were approximately 1000 bases, one of ordinary skill in the art, coupled with the knowledge in the art that PCR is biased toward shorter fragments, would have had a reasonable expectation of success at producing a DNA library which maintained 85% or more of genome representation employing the method of Oefner et al. which allowed the generation of shorter nucleic acid fragments.

Finally, Applicants contend that Oefner et al. and Lucito fails to suggest or disclose the particular average size from 0.5 kbp to 2.5 kbp according to the presently claimed invention, and thus, *prima facie* case of obviousness has not been established (page 10, 1st paragraph, Response).

This argument is not found persuasive because the desire to generate a DNA library which represent the entire genome is well established as well as explicitly suggested by Lucito et al. as already discussed above).

The fact that Lucito et al. were able to generate by amplification a library which maintains approximately 75% of the genome (based on fragments of approximately 1000 bps), has been plainly evidenced.

The fact that Oefner et al. was able to generate shorter random DNA fragments than those of Lucito et al. have been also made plainly evident.

The fact that shorter nucleic acid fragments are amplified better in amplification reaction has also been made plainly evident by Lucito et al.

Thus, one of ordinary skill in the art would have been reasonably motivated to combine the teachings to generate a DNA library which represent more of the genome. Based these teachings and knowledge of the art, arriving at a DNA library of the requisite representation would also be considered as routine optimization (see MPEP 2144.05(II)(A)).

For the above reasons, the arguments are not found persuasive and the rejection is maintained.

The rejection of claims 17-21 under 35 U.S.C. 103(a) as being unpatentable over Oefener et al. (Nucleic Acids Research, 1996, vol. 24, no. 20, pages 3879-3886) in view of Lucito et al. (PNAS, 1998, vol. 95, pages 4487-4492) as applied to claims 7-16 above, and further in view of Sorge et al. (U.S. Patent No. 5,556,772, issued September 17, 1996), made in the Office Action mailed on November 14, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on February 14, 2006 have been fully considered but they are not found persuasive.

Applicants do not provide any new arguments, but rather rely on the arguments which were fully discussed above, and which were found non-persuasive.

The rejection is maintained therefore.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
3/31/2006

YOUNG J. KIM
PATENT EXAMINER

yjk